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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,990	BRAHMBHATT ET AL.	
	Examiner	Art Unit	
	ANOOP SINGH	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *19-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18, 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/16/07; 6/7/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the papers filed December 15, 2008. Applicant's response to restriction requirement to the claims filed December 15, 2008, has been entered. Currently, claims 1-35 are pending.

Election/Restrictions

Applicants' election of claims 1-18 and 35 (Group I) in the reply filed on December 15, 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Applicants have also elected polypeptide as species for bispecific ligand. Upon further consideration election of species requirement is withdrawn and all the species of bispecific ligand is rejoined for the examination purpose.

Claims 19-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on December 15, 2008. As the restriction is deemed proper, the requirement for restriction is hereby made FINAL.

Claims 1-18 and 35 are under current examination.

Information Disclosure Statement

Applicants' IDS, filed 06/07/2006 and 07/16/2007 have been considered. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a

separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered. In the instant case, applicants have cited multiple references in the specification but they have not been considered by the Examiner as no copy of any of the publication was provided.

Claim Objections

Claim 18 is objected to because of the following informalities: Claim 18 does not end with a period. Appropriate correction is required.

Claim 2-18 are objected to because of the following informalities: In the instant case, series of singular dependent claims 2-18 recite article "a method.." that appears to be depend on multiple claims. However, claims 2-18 directly or indirectly depend on claim 1. Therefore, article of all the dependent claims should be changed to "The method of" (for example see MPEP 608.01(n) part IV under Claim form and arrangement). Appropriate correction is required.

Claim 35 is objected to because of the following informalities: an independent claim must start with an article "a" and, therefore, claim 35 should recite "A method of using..". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 and 35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a targeted gene delivery method comprising bringing bispecific ligands into contact with (a) bacterially derived minicells that contain a nucleic acid sequence encoding a therapeutic protein operably linked to a promoter and (b) non-phagocytic mammalian cells, such that (i)

said bispecific ligands cause said minicells to bind to said mammalian cells and (ii) said minicells are engulfed by said mammalian cells, which produce an expression product of said nucleic acid sequence,

does not reasonably provide enablement for delivering a nucleic acid that is not operably linked to a promoter to produce an expression product or use of medicament comprising minicells and bispecific ligand for modifying any trait or treat any disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

The claims are directed to a targeted gene delivery method that comprises bringing bispecific ligands into contact with (a) bacterially derived minicells that

contain a therapeutic nucleic acid sequence and (b) non-phagocytic mammalian cells, such that (i) said bispecific ligands cause said minicells to bind to said mammalian cells and (ii) said minicells are engulfed by said mammalian cells, which produce an expression product of said therapeutic nucleic acid sequence. The subsequent claims limit the method to include a therapeutic nucleic acid sequence encoding a suicide gene. Claim 35 is directed to a method of using of bacterially derived intact minicells and bispecific ligands in the preparation of a medicament in a method of treating a disease or modifying a trait by administration of said medicament to a cell, tissue, or organ.

The invention relates to targeting bacterial minicell vectors to non-phagocytic host cells by employing bispecific molecules that specifically bind to both a minicell surface structure and a host cell surface structure, such as a receptor. Thus, by mediating an interaction between the minicell vectors and non-phagocytic host cells, the bispecific ligands enable targeted delivery of polynucleotide to the host cells (see specification, page 1). Applicant's specification encompasses a plethora of wide-ranging uses of such minicells, by using bispecific antibody ligands with anti-O-polysaccharide specificity on one arm and anti-HER2 receptor, anti-EGF receptor or anti-androgen receptor specificity on the other arm efficiently bound minicells to the respective receptors on a range of non-phagocytic cells. These cells included lung, ovarian, brain, breast, prostate and skin cancer cells (page 11). In addition, the specification contemplates performing *ex vivo* gene therapy into desired non-phagocytic mammalian cells that are normally refractory to minicell-mediated gene therapy (page 23). The specification also discloses other uses of minicells in treatment of various conditions and diseases, to increase the expression of a desired protein, to inhibit expression or function of a gene product, and so forth including in treating cancer or an acquired disease, such as AIDS, pneumonia, emphysema, or in correcting inborn errors of metabolism, such as cystic fibrosis, other embodiments include downstream product of post-translational modification of the expression

product, that reduces the immunologic sequalae related to transplantation or that helps facilitate tissue growth and regeneration (page 24 of the specification). In view of general teaching in the specification, for purposes of the rejection, the common themes of all these *in vivo* methods is the ability to target and express genes, whether locally or within a cell which the minicell transforms. However, considering the wide range of diseases and disorders of different pathology and etiology encompassed, and wide range of methods of administration, along with the wide range of mechanisms by which such therapy may be effected, and given that Applicant has not provided specific guidance and direction that would overcome lack of reasonable predictability in a predictable animal model and the state of the art, the Artisan would have to perform undue experimentation to reasonably predict working embodiment encompassed by Applicant's claims commensurate with full scope of the claims.

The invention is in the nature of the specific targeting of cell populations to affect localized binding and expression of therapeutic genes, and the transformation of tissues with genes, to effect gene therapy. Therefore, an in-depth analysis of gene itself will suffice to review the nature of the invention, as the same requirements to effect gene therapy are also part of the other methods. Specifically, as will be shown below, the ability to target, binding, express enough mRNA and protein therefrom, for a long enough time to affect such therapy is required of these inventions. This is particularly important since the state of the art effectively summarized by the reference of Verma (Annu Rev Biochem. (2005), 74:711-38) describes progress and failures in achieving the desired effects after gene therapy suggesting vector targeting *in vivo* to be unpredictable and inefficient as numerous factors complicated the gene delivery art that is difficult to be overcome by routine experimentation. These include, the fate of DNA vector itself, volume of distribution, rate of clearance in tissue, the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell

population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of RNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ significantly based on the vector used and the protein being produced (Ecke, Goodman & Gilman's The Pharmacological basis of Therapeutics, 1996, McGraw-Hill, New York, NY. pp 77-101, especially page 81-83). In view of foregoing, it is apparent that the art for gene therapy in general is marred by several problems, and the art for minicells for gene therapy being less advanced than that of other vectors (viral), would have similar difficulties of gene transduction to attain therapeutic effective level for desired time to exert therapeutic effect. The prior and post filing art demonstrates a need for much more in the way of guidance and examples to enable any aspect of minicell gene therapy. It is noted that although prior art teaches delivery of defective - bacterial cells as a vector for the delivery of genes into mammalian cells, thereby inducing an immune response. Grillot-Courvalin et al (Cell Microbiology 2002; 4(3):177-86) reported gene transfer *in vivo* in mice *and in vitro* from intracellular bacteria to mammalian phagocytic and non-phagocytic cells. It is reported that gene transfer efficiency is markedly dependent on the type of recipient cell (see page 182, co. 2, last para.).Therefore, the art at the time of invention by applicant the art did not enable treating genus of condition of different etiology and pathology by delivering intact minicells of the invention because such minicells had only been used to transfer DNA *in vitro*, but did not result in treatment of any condition. Therefore, outside of *in vitro* transformations or *in vivo* site specific delivery using membrane fusion methods, such minicells are not enabled for treating any condition by delivering a plasmid to treat any condition. The *in vivo* methods of treating plurality of different conditions are non-enabling due to same problems of expressing gene of interest at a level sufficient in the target for the reasons discussed above.

The independent claims as recited do not require the polynucleotide encoding therapeutic protein to be part of an expression vector operably linked to any promoter that permits the expression of said nucleic acid molecule in non phagocytic mammalian cells. Given the broadest reasonable interpretation, independent claim embraces delivering minicell comprising nucleic acid without any regulatory sequence directly to the cells of the subject under *in vitro* or *in vivo* condition. The specification provides guidance with respect to using a mammalian gene expression vector that expresses the HSV1tk::Sh fusion gene under the control of the EF-1alpha./eIF4γ hybrid promoter (example 1). However, the specification does not provide guidance on the use of naked nucleic acid molecules, lacking a promoter or other regulatory sequences in the claimed method. Further, the literature at the time of filing does not provide guidance on how to get RNA polymerase to efficiently prime to a DNA strand that lacks a promoter. In fact, De Palma (Hum Gene Ther. 2003; 14(12): 1193-206) describes the efficiency and specificity of vector expression *in vitro* in a panel of human primary cultures. The vectors containing promoter and enhancer sequences from the gene showed cell specific expression *in vitro* and *in vivo* while the PGK or CMV promoter gave widespread GFP marking in endothelial and non-organs. Therefore, it is apparent that a delivery of polynucleotide encoding therapeutic protein without any promoter or regulatory sequence would not provide cell specific expression of transgene. In the instant case, specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to how an artisan of skill would have practiced the claimed method would have resulted in expression product in a mammalian cell as embraced by the breadth of the claims.

The specification broadly outlining various compositions of minicells and provide guidance with respect to efficient binding and receptor-mediated internalization of bispecific antibody-targeted minicells into non-Phagocytic human prostate carcinoma cells (example 1), human breast adenocarcinoma cells (example

2) and human ovarian carcinoma cells (example 3) under *in vitro* condition. The specification also teach recombinant minicells carrying a plasmid encoding HSVtk gene that could effect regression of human breast cancer cell tumor xenografts in an athymic nude mice (example 5-7 and figure 5-7). The results reveal a significant stabilization/regression of the established tumors only in mice treated by intratumoral delivery of EGFR-targeted minicellsHSV1tk. In essence, Applicant has provided a large amount of information that provides adequate guidance with respect to indicated enabling embodiment of gene transfer by minicell to mammalian cells. The specification fails to provide enabling disclosure for a method of treating genus of disease or improving trait by administering minicell of the invention via any route to gene transfer in any mammalian cell of any subject.

The claim 35 is directed to use of minicells and bispecific ligand in the preparation of a medicament that is capable of binding to target mammalian cell in treating any disease by administering the medicament via any route to any cell, tissue or organ. Applicant's envisioned and presently claimed methods embodiments are for any cell type, any method of administration, and any minicell vector, to treat or modify any trait in any subject. The specification teaches that targeted recombinant minicells are capable of successfully deliver the HSV1tk gene encoding plasmid to the xenografted tumor cells. The tumor volumes in this group did not increase in size and remained stable throughout the course of the experiment (see example6, figure 5). However, the specification fails to provide any evidence that nucleic acid encoding any therapeutic protein could be delivered at therapeutic effective level to elicit a pharmacological response in specifically reducing tumor in an experimental model. This is due to susceptibility and outcome in complex disorders such as cancer are determined, at least in part by genetic polymorphism, and considerable difficulties remain in elucidating how different genes determine a particular phenotype. The etiology of cancer is multifactorial, and it is likely to involve the actions of genes at multiple levels along the multistage carcinogenesis

process (see Carbone et al. Seminars in Cancer Biology, 2004, 14: 399-405, entire article). This is partly because advanced solid tumors are genetically heterogeneous both among cases and within the same patient. The art of gene transfer based methods as therapeutics against cancer was known to be unpredictable with respect to efficiency and selectivity, i.e., discrimination between tumor and normal cells. The problems with cell-based screening methods for chemotherapeutic agents are well known in the art, particularly with regard to forecasting aspects such as *in* vivo efficacy, targeted delivery to the tumor site, and selective killing of tumor cells. With respect to *in* vivo efficacy, Kunz-Schughart et al. (Journal of Biomolecular Screening, 2004, 9:273-285) teach "[A]lthough cell-based screening is established in the drug discovery process, particularly in the many well-described cell line models for cancer, its value in predicting clinical response to new agents is limited. This lack of predictability of commonly employed 2-dimensional (2-D) cellular assays is attributable to the fact that such systems do not mimic the response of cells in the 3-D microenvironment present in a tissue, or tumor, *in vivo*. [M]any of the current *in vitro* systems for cell-based screening and target validation remain unreliable and non predictive for clinical efficacy. Kunz-Schughart et al describes "the choice of medium and medium supplements, cell density, and the composition of the culture surface have a critical impact on cell proliferation, differentiation, migration, and death by affecting intracellular signal transduction." Thus efficacy of gene transfer using minicell in tumor cells under *in vitro* condition would not provide any reliable information to an artisan to extrapolate the *in vitro* data to a method of treating genus of disease including plurality of different cancer embraced by the breadth of the claims. Regarding the use of nude mice as the *in vivo* model of human cancer, prior and post filing reference summarized by the references of Kelland et al (European Journal of Cancer, 2004, 40, 827-836) and Kerbel (Cancer & Metastasis Rev. 17:301-304; 1999) list several variables that impact on outcome; viz, site of implantation, growth properties of the xenograft and size when treatment is

initiated, agent formulation, scheduling, route of administration and dose and the selected endpoint for assessing activity (Kelland, abstract). It is noted that "[m]ost transplantable tumor therapy experiments utilize ectopic (usually subcutaneous) injection and growth of the cells. The positive responses of such tumors to certain anti-cancer drugs or therapies have been questioned, and at least in some cases it has been shown that orthotopically transplanted tumors do not necessarily recapitulate the 'encouraging' responses of their ectopically grown counterparts… The response to therapy of a single 'primary'(usually ectopic/subcutaneous) growing transplanted tumor mass is usually what is evaluated rather than that of distant metastases growing in visceral organs such as the brain, lungs, or liver. Given recent findings that various properties of tumor cells can be influenced by the organ microenvironment, there is clearly a need to place more emphasis on tumor models in which metastases are the primary target of therapy, and not just a transplanted 'primary' tumor." (Kerbel et al, page 301, col. 1). In the instant case, Applicants have not utilized primary tumor cells or immunocompetent model and have further administered the cells hetertopically. The specification is silent on the description for orthotopic administration of the cell lines in an immunocompetent animal model and is further silent on the detection of micro-metastases of any tumors, to any sites, including bone marrow. As the culture modified cell lines described do not constitute human primary tumor cells, or the morphological characteristics of cancers, together with the lack of orthotopic transplantation of cells, the metastases described fail to adequately reflect or simulate the progression of genus of cancer of different etiology and pathology. This clearly establishes the unpredictability of the animal models extrapolated to the breadth of the claim directed to treating any condition and thus findings in immunodeficient mice xenograft model by administering minicell cannot be directly extrapolated to effect of administering the claimed minicells in any subject via any route because it is evident that the artisan would require, making and/or using a new invention in the field. The specification

also does not provide any guidance as to how studies in animal model can be extrapolated to genus of condition as embraced by the breadth of the claims. Moreover, the art at the time of invention by applicant does not disclose any examples of *in vivo* therapy in a predictable immunocompetent model using minicells of any type; therefore, the art of minicells is not any more enabling than that of gene therapy in general. An artisan would have to carry out extensive experimentation to make use of the invention, and such experimentation would have been undue because of the art of using minicell for gene therapy to treat any disease or modifying any trait is unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced.

The scope of invention as claimed encompasses a method of administering the intact minicell composition of the invention via any or all route including locally, systemically, oral administration, inhalation or insufflation, or parenteral, intramuscular, intravenous, intraportal, intrahepatic, peritoneal, subcutaneous, intratumoral, or intradermal administration (see specification page 25, para. 2). The guidance provided in the specification is limited to intratumoral administration of minicell to target tumor cells in the mouse. However, prior art teaches that it is difficult to predict the efficacy and outcome of transduced naked DNA encoding the protein because several factors influence the resulting outcome. The transduction of target cells, type of target cells and choice and/or characteristics of delivery vectors, route and site of delivery are some of the important determinant that influences the outcome upon administration of any DNA. Prior to instant invention, McCluskie et al (Mol. Med. 19995:287-300; Abstract) observed lack of response to non-injected routes of administration of DNA based vaccines, such as oral routes, sub lingual, inhalation and vaginal wall due to variation in transfection efficiency (Abstract). Thus, it is apparent that transduction of target cells represents the first critical step in any gene based therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vehicle. For instance, Lu et al

(Cancer Gene Ther. 1999 Jan-Feb; 6(1): 64-72) while reviewing the state of art of efficacy of delivery by various routes in prostate describe three routes of delivery (i.t., i.a., and i.v.) to compare in the canine model to determine the transduction efficiency with the lowest systemic dissemination. Lu et al conclude that all three-delivery routes resulted in variable degree of gene transduction (see page 70, column 2, last paragraph to page 71, column 1, paragraph 1). Although, Lu et al do not show treatment of any tumor by delivering intact minicell as vector but they clearly demonstrate variable pattern often seen when vector is administered via different route. The specification and prior art do not teach a method for treating plurality of different condition in an animal model, from which data could be extrapolated to the breadth of the claim. Given the lack of guidance provided by the specification, one of skill in the art would be left to speculate as to the conditions and/or steps necessary for treating disorder of different etiology and pathology. It would have required undue experimentation for one of skill in the art to make and use the invention as claimed without a reasonable expectation of success.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to make and/or use the invention claimed over its full scope. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the lack of working examples provided, the amount of experimentation necessary, the scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in

> section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 7-18 and 35 are rejected under 35 U.S.C. 102(e) as being anticipated by Sabbadini et al. (US 7,183,105, dated 2/27/2007, filed 5/28/2002, effective filing date 2/25/2002).

Claims are directed to a targeted gene delivery method that comprises bringing bispecific ligands into contact with (a) bacterially derived minicells that contain a therapeutic nucleic acid sequence and (b) non-phagocytic mammalian cells, such that (i) said bispecific ligands cause said minicells to bind to said mammalian cells and (ii) said minicells are engulfed by said mammalian cells, which produce an expression product of said therapeutic nucleic acid sequence. Subsequent claims limit the method of 1 wherein said bispecific ligand comprises polypeptide or carbohydrate and wherein said bispecific ligand comprises a first arm that carries specificity for a bacterially derived minicell surface structure and a second arm that carries specificity for a non-phagocytic mammalian cell surface receptor. Claims further limit the method according to base, wherein mammalian cell surface receptor is capable of activating receptor-mediated endocytosis of said minicells. Claim 9 limits the bispecific ligand of claim 1 to include an antibody or antibody fragment. Claim 11 limits the minicells of claim 1 to an intact cell wall. Claims 14 and 15 limit the method wherein mammalian cells are under *in vitro* or *in vivo* condition. Claim 35 is included in the rejection because of the breadth of the claims. The rejection is applied to the extent method only requires administering minicells containing a therapeutic nucleic acid and a bispecific ligand that is capable of binding minicells and target non phagocytic mammalian cell. The rejection is not to a method of treating a disease or modifying trait. It is noted that specification teaches useful ligands include receptors, enzymes, binding peptides, fusion/chimeric proteins and small molecules. The bispecific ligand comprising first arm that carries specificity for minicells surface and a second arm that carries

specificity for cell surface receptor has been interpreted as being equivalent to the attachment of an antibody that binds to a ligand specific to a minicell as well as receptor on to the mammalian cell surface, as first and second arm respectively.

With respect to claims 1-4, 7-9, Sabbadini et al. teach a gene delivery method comprising contacting a mammalian cell with a bacterial minicells comprising a therapeutic agent that is coated with an antibody as a binding moiety that specifically binds a ligand present on the surface of said mammalian cell such that the contents of the minicells are delivered into the cell from a minicell bound to the cell. Sabbadini teaches that the active agent is a nucleic acid (see column 7, line 1-12 and col. 17, 6-15, col. 136, lines 58-66) and the target mammalian cell may include cos or A-431 cancer cell line that are non phagocytic mammalian cell (column 252, line 30 and 55). It is also disclosed that the receptor/ligand interaction will result in the endocytosis of the minicell into the target cell where the minicell would release and deliver the genetic material (see col. 164, lines 28-37). The compound to be conjugated to the minicells can be a polypeptide or a lipid. It is also disclosed that an antibody can be covalently attached as a binding moiety (see column 136, lines 58-66) that binds to ligand present on the surface of a mammalian cell. Furthermore, Sabbadini et al teach attaching compounds-or moieties to minicells via membrane proteins that are displayed on the minicells (see col.4 and 5). Thus, the antibody displayed on the surface of the minicell attaches to cell surface receptor would be monospecific to first and second arm respectively. It is also disclosed that the minicells containing genetic material targets cells by using either receptor mediated endocytosis or phagocytosis (col. 159 lines 4-6, 38, line 18) meeting the limitation of claims 1-4, 7-9. Additionally, Sabbadini et al teach that the antibody may be a single chain antibody (see col. 132, line 60) or a humanized antibody (col. 132, line 53) (limitation of claim 10). With respect to claim 11, Sabbadini et al disclose that the minicells produced contains an intact cell wall (see col. 39, lines 34-35, and claims 1, 8 in '105). Regarding claims 12-13, Sabbadini et al

contemplates a method to deliver expression plasmids that could correct protein expression deficiencies or abnormalities as in cystic fibrosis by delivering nucleic acid encoding chloride channel (see col. 167, lines 35) or DNA to kill the cell (see col. 38, line 13). Sabbadini et al. also teach that minicells may also be use to deliver antisense oligonucleotide to the target cell (see column 167, lines 20-23). With respect to claims 14-15, Sabbadini et al. teach that method of gene transfer that may occur between minicells and a mammalian cell under *in vitro* or *in vivo* condition (see col. 251, lines 40-43). Regarding claims 16-18, Sabbadini et al. teaches minicells comprising first and second nucleic acids and wherein each nucleic acid comprises expression sequences (see columns 25, lines 4-14). Sabbadini et al. disclose that nucleic acids of the invention can be delivered by minicells containing plasmids or expression vectors comprising sequences encoding the nucleic acids, wherein the expression constructs comprise regulatory elements operably linked to a nucleotide sequence that serves as a template for a bioactive nucleic acid (see column 17 and example 19). Sabbadini et al. teach that a minicell of the invention comprises at least one nucleic acid, wherein the nucleic acid comprises an expression construct comprising expression sequences operably linked to an ORF encoding a protein (see column 23, line 48-52, column 24, lines 1-3). Sabbadini et al. teach plasmid pMPX-6 comprising nucleic acid encoding reporter protein (EGFP) under the control of CMV promoter to monitor the efficiency of gene transfer (example 19). With respect to claim 35, Sabbadini et al teach administering minicells containing genetic material to target host mammalian cells (col. 159 lines 4-6, column 167, lines 30-45).

Accordingly, Sabbadini et al anticipates claims 1-4, 7-18 and 35.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 5-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sabbadini et al. (US 7,183,105, dated 2/27/2007, filed 5/28/2002, effective filing date 2/25/2002), Nettelbeck et al (Mol Ther. 2001; 3(6):882-91, IDS) and Coldwell et al (The Journal of Immunology, 1984, 133, 2 950-957).

Claims are directed to a targeted gene delivery method that comprises bringing bispecific ligands into contact with (a) bacterially derived minicells that contain a therapeutic nucleic acid sequence and (b) non-phagocytic mammalian cells, such that (i) said bispecific ligands cause said minicells to bind to said mammalian cells and (ii) said minicells are engulfed by said mammalian cells, which produce an expression product of said therapeutic nucleic acid sequence. Claim 3 limits the method of 1 wherein said bispecific ligand comprises polypeptide or carbohydrate and wherein said bispecific ligand comprises a first arm that carries specificity for a bacterially derived minicells surface structure and a second arm that carries specificity for a non-phagocytic mammalian cell surface receptor.

Claim 5 is method according to claim 3, wherein first and second arm are multivalent and wherein said minicell surface structure s an O-polysaccharide component of a liposaccharide on minicell cell surface.

With respect to claims 1, 3, Sabbadini et al. teach a gene delivery method comprising contacting a target mammalian cell with a bacterial minicells containing a therapeutic agent that is coated with an antibody as a binding moiety that specifically binds a ligand present on the surface of the target mammalian cell such that the contents of the minicells are delivered into the cell from a minicell bound to the cell. It is also disclosed that the active agent is a nucleic acid (see column 7, line 1-12 and col. 17, 6-15, col. 136, lines 58-66) and the target mammalian cell may include cos or A-431 cancer cell line that are non phagocytic mammalian cell (column 252, line 30 and 55). Sabbadini et al. teach that the receptor/ligand interaction will result in the endocytosis of the minicell into the target cell where the minicell would release and deliver the genetic material in the target cell (see col. 164, lines 28-37). Furthermore, Sabbadini et al teach attaching binding compounds-or moieties to minicells via membrane proteins that are displayed on the minicells. The compound to be conjugated to the minicells can be a polypeptide. It is also disclosed that an antibody can be covalently attached as a binding moiety (see column 136, lines 58-66). It is also disclosed that the minicells containing genetic material targets cells by using either receptor mediated endocytosis or phagocytosis (col. 159 lines 4-6, 38, line 18).

Although, Sabbadini et al. teach a method of gene delivery by covalently attaching binding moieties including antibody to minicells via membrane proteins that binds to a ligand present on the surface of a mammalian cell, but differed form claimed invention by not explicitly disclosing that the first arm binding to minicell surface is an O-polysaccharide component of LPS or first and second arm are multivalent.

However, prior to instant invention, Nettelbeck et al teach a recombinant antibody as a molecular bridge, linking the adenovirus capsid to the endothelial cell surface protein endoglin, for vascular targeting of adenoviruses (abstract). It is noted that Nettelbeck et al also disclose a method to construct bispecific single chain diabody directed against endoglin and the adenovirus knob domain (see 885, col.1, para.4). It is also disclosed that the ScFv C4 (endoglin) and the neutralizing anti-knob scFv S11 are combined in a single-chain diabody (scDb EDG-Ad) (see figure 3) for experimental analysis. Nettelbeck et al reported enhanced adenoviral infectivity mediated by scDb EDG-Ad that was restricted to endoglin-positive cells showing cell specific targeting (see figure 6, page 889, col. 2, para. 2).

Although Nettelbeck et al describes the advantage of using single chain diabody to target adenoviral fiber knob domain to endoglin expressing cancer cell, but differed from claimed invention by not disclosing first arm specific to O-polysaccharide of a LPS.

Prior to instant invention, Coldwell et al teach production of monoclonal antibodies to antigenic determinants of the O-polysaccharide of *Salmonella typhimurium* lipopolysaccharide (LPS) (abstract).

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine the respective teachings of Sabbadini et al, Nettelbeck et al and Coldwell by using an single chain dibody (bivalent bispecific antibody) to bring together intact minicell and mammalian cell such that minicell binds to mammalian cell and minicell that are engulfed by the mammalian cell with a reasonable expectation of success, at the time of the instant invention. A person of skill in the art would have been motivated to use an antibody as a molecular bridge, linking the O-polysaccharide of the minicell to the endothelial cell surface protein endoglin (diabody) as a matter of design choice to obtain more specific delivery of therapeutic agent as described by Nettelbeck, said design choice amounting to combining prior art elements according to known methods to yield predictable

results. One who would have practiced the invention would have had reasonable expectation of success since Sabbadini et al had already taught a method for gene transfer by attaching a bacterial minicells with an antibody that specifically binds a ligand present on the surface of a mammalian cell, while combining the teaching of Sabbadini et al with those of Nettelbeck and Coldwell would have resulted in specific gene transfer into endoglin positive endothelial cell.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-18 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 28, 48-54 of copending Application No. 12/053,197. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are

directed to overlapping subject matter. Claims in the instant application are directed to a targeted gene delivery method that comprises bringing bispecific ligands into contact with (a) bacterially derived minicells that contain a therapeutic nucleic acid sequence and (b) non-phagocytic mammalian cells, such that (i) said bispecific ligands cause said minicells to bind to said mammalian cells and (ii) said minicells are engulfed by said mammalian cells, which produce an expression product of said therapeutic nucleic acid sequence. Subsequent claims limit the method of 1, wherein said bispecific ligand comprises polypeptide or carbohydrate and wherein said bispecific ligand comprises a first arm that carries specificity for a bacterially derived minicell surface structure and a second arm that carries specificity for a non-phagocytic mammalian cell surface receptor. Claims further limit the method of claim 1, wherein mammalian cell surface receptor is capable of activating receptor-mediated endocytosis of said minicells. Claim 9 limits the bispecific ligand of claim 1 to include an antibody or antibody fragment. Claim 11 limits the minicells of claim 1 to an intact cell wall. Claims 14 and 15 limit the method wherein mammalian cells are under *in vitro* or *in vivo* condition. In contrast, claim in 28, 48-54 of copending Application No. 12/053,197 are directed to a method of delivering functional nucleic acid, comprising (a) providing a plurality of intact minicells in a pharmaceutically acceptable carrier, each minicell of said plurality encompassing functional nucleic acid, and (b) bringing minicells of said plurality into contact with mammalian cells such that said mammalian cells engulf minicells of said plurality, whereby said functional nucleic acid is released into the cytoplasm of the target cells, wherein step (b) entails bringing a bispecific ligand into contact with at least some of said intact minicells and said target mammalian cell, such that said bispecific ligand causes minicells to bind to said mammalian cell. Claims 49-50 limit the method of claim 48, wherein said target mammalian cell is a non-phagocytic cell and said bispecific ligand comprises a first arm that carries specificity for a minicell surface structure and a second arm that carries specificity

for a non-phagocytic mammalian cell surface receptor. Claims 51-52 are directed to method of claim 50, wherein said minicell surface structure is an O-polysaccharide component of a lipopolysaccharide on said minicell surface and wherein said mammalian cell surface receptor is capable of activating receptor-mediated endocytosis of said minicell. Subsequent claims limit the method of claim 48, wherein said bispecific ligand comprises an antibody or antibody fragment and said mammalian cell is phagocytosis- or endocytosis-competent. It is noted that claims in the instant application differ only with respect to a broader scope of nucleic acid, which encompasses those specifically claimed in application '197. Each of the claim sets are directed to a method that involves intact bacterial cells with overlapping methods. The claims of application '197 and the instant claims are considered obvious in view of each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1 and 15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-7 of copending Application No. 10/492,301. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are directed to overlapping subject matter. The claims of application '301 are directed to a genetic transformation method comprising (i) providing a preparation comprising recombinant, intact minicells that contain a plasmid comprising a nucleic acid sequence, wherein said preparation contains; and (ii) bringing said preparation into contact with mammalian cells that are phagocytosis- or endocytosis-competent, such that said minicells are engulfed by said mammalian cells, whereby said mammalian cells produce an expression product of said first nucleic acid sequence. Claims 7limits the mammalian cells are *in vivo.* Each of the elements of the claims of application '301 are elements of the instant

claims. Each of the claim sets are directed to a method of gene transfer using minicells with overlapping structural components. The claims of application '301 and the instant claims are considered obvious in view of each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1 and 15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-7 of copending Application No. 12/019,090. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are directed to overlapping subject matter. The claims of application '090 are directed to a genetic transformation method comprising (i) providing a preparation comprising recombinant, intact minicells that contain a plasmid comprising a nucleic acid sequence, wherein said preparation contains; and (ii) bringing said preparation into contact with mammalian cells that are phagocytosis- or endocytosis-competent, such that said minicells are engulfed by said mammalian cells, whereby said mammalian cells produce an expression product of said first nucleic acid sequence. Claims 7limits the mammalian cells are *in vivo.* Each of the elements of the claims of application '301 are elements of the instant claims. Each of the claim sets are directed to a method of gene transfer using minicells with overlapping structural components. The claims of application '301 and the instant claims are considered obvious in view of each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-18 and 35 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 37-41, 43-47, 48, 50-54 and 73 of copending Application No. 11/765,635. Although the conflicting

claims are not identical, they are not patentably distinct from each other because the claims are directed to overlapping subject matter. Claims in the instant application are directed to a targeted gene delivery method that comprises bringing bispecific ligands into contact with (a) bacterially derived minicells that contain a therapeutic nucleic acid sequence and (b) non-phagocytic mammalian cells, such that (i) said bispecific ligands cause said minicells to bind to said mammalian cells and (ii) said minicells are engulfed by said mammalian cells, which produce an expression product of said therapeutic nucleic acid sequence. Subsequent claims limit the method of 1, wherein said bispecific ligand comprises polypeptide or carbohydrate and wherein said bispecific ligand comprises a first arm that carries specificity for a bacterially derived minicell surface structure and a second arm that carries specificity for a non-phagocytic mammalian cell surface receptor. Claims further limit the method of claim 1, wherein mammalian cell surface receptor is capable of activating receptor-mediated endocytosis of said minicells. Claim 9 limits the bispecific ligand of claim 1 to include an antibody or antibody fragment. Claim 11 limits the minicells of claim 1 to an intact cell wall. Claims 14 and 15 limit the method wherein mammalian cells are under *in vitro* or *in vivo* condition. In contrast, claim in 37-41, 43-48, 50-54 and 73 of copending Application No. 11/765635 is directed to a nucleic acid delivery method that comprises bringing bispecific ligands into contact with (a) intact bacterial cells that contain a therapeutic nucleic acid sequence and (b) non-phagocytic mammalian cells, such that (i) said bispecific ligands cause said cells to bind to said mammalian cells and (ii) said bacterial cells are engulfed by said mammalian cells, which produce an expression product of said therapeutic nucleic acid sequence. Claims 38 and 39 limit the method of claim 37, wherein the mammalian cells are in vitro and in vivo respectively. Claim 40 is directed to a targeted drug delivery method that comprises bringing bispecific ligands into contact with (a) bacterial cells that contain a drug molecule and (b) target mammalian cells, such that (i) said bispecific ligands cause

said bacterial cells to bind to said mammalian cells, (ii) said bacterial cells are engulfed by said mammalian cells, and (iii) said drug is released into the cytoplasm of said mammalian cells, wherein said target mammalian cells are non-phagocytic cells. Claims 43-44 limit the method of claim 40 to include, wherein said mammalian cells are in vitro and in vivo respectively. Claim 45 limits the method of claim 40, wherein said drug is encoded on a plasmid contained within said bacterial cells that may include plasmid comprises a regulatory element. Claim 47 is directed to method of claim 45, wherein said plasmid comprises a reporter element. Claims 73 is directed to use of bacterial cells and bispecific ligands in the preparation of a medicament, said bacterial cells containing a therapeutic nucleic acid, and said bispecific ligands being capable of binding to said bacterial cells and to target non-phagocytic mammalian cells, for use in a method of treating a disease or modifying a trait by administration of said medicament to a cell, tissue, or organ. It is noted that claims in the instant application differ only with respect to a broader scope of nucleic acid, which encompasses those specifically claimed in application '635. Each of the claim sets are directed to a method that involves intact bacterial cells with overlapping methods. The claims of application '635 and the instant claims are considered obvious in view of each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Tomlinson I et al (.Methods Enzymol, 2000, 326, 461-479) teach a method for generating multivalent and bispecific antibody fragments.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANOOP SINGH whose telephone number is (571)272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Anoop Singh/
Examiner, Art Unit 1632